Differential expression of fatty acid-binding proteins and pathological implications in the progression of tongue carcinoma

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Received July 10, 2013; Accepted September 12, 2013

DOI: 10.3892/mco.2013.198

Abstract. Tongue carcinomas are common malignancies of the oral cavity. Understanding the molecular mechanisms behind the disease progression is a prerequisite for improving patient prognosis. Fatty acid-binding proteins (FABPs) are cytoplasmic lipid chaperones that affect cellular organization and energy production. Although their aberrant expression is involved in carcinoma progression, its role in the pathology of tongue carcinomas remains unclear. In the present study, the immunohistochemical expression of FABP4 and FABP5 in tongue carcinomas (n=58) and its involvement in the clinicopathological parameters were examined. Normal tongue epithelial cells expressed FABP5, an epidermal-type FABP, but not FABP4, an adipocyte-type FABP. The cytoplasmic staining of FABP5 was increased in carcinomas with advanced T-stage ($P<0.05$) and clinical stage ($P<0.05$). Ectopic expression of FABP4 was detected in almost all carcinomas, although its role in disease progression remains undetermined. Upregulation of FABP5 in the wounded skin of genetically normal mice indicated that microenvironmental tissue factors induce FABP5 expression. The results of the present study demonstrated the aberrant expression of FABP4 and FABP5 in tongue carcinomas and suggested the involvement of FABP5 in disease progression.

Introduction

Squamous cell carcinoma developing from the oral cavity is a common malignant neoplasm of the head and neck, with tongue carcinomas accounting for 25-40% of all oral carcinomas (1,2). Over 50% of patients experience a relapse and the incidence is expected to increase in the next few decades (3). Carcinoma cells exhibit marked changes in cellular composition, signaling and energy metabolism, and these changes lead to advanced stages of progression (4,5). Identification of molecular aspects of carcinoma cells contributes to the development of novel therapeutic approaches and improves patient prognosis.

Carcinoma cells change the lipid composition of cell membranes (6) and stimulate lipid metabolism during tumor progression (7). Fatty acid-binding proteins (FABPs) are the lipid chaperones that transport long chain fatty-acids (LCFAs) to specific cell compartments, such as lipid droplets for storage; the endoplasmic reticulum for signaling, trafficking and membrane synthesis; mitochondria or peroxisomes for oxidation; cytosoles or other enzymes for activity regulation; the nucleus for gene transcription; or even outside of the cells in order to signal in an autocrine or paracrine manner (8,9). The FABP family consists of at least nine members that were originally identified in different cell or tissue types, such as FABP4 in adipocytes and FABP5 in the epidermis (10,11). Studies have revealed the involvement of aberrant FABP expression in the pathology of various diseases including malignant neoplasms (8,9). Although FABP5 is reported to be upregulated in oral carcinomas, its involvement in disease progression remains controversial (11-13).

The ectopic expression of FABP4 in carcinomas of the stomach (14) and ovary (15) facilitates disease progression, whereas it is downregulated in aggressive subsets of bladder and breast carcinomas (16-18). These data suggest the differential role of FABP4 in carcinomas depending on the tissue origin. FABP4 expression in oral carcinomas requires elucidation. Therefore, in this study, we examined FABP4 and FABP5 expression in tongue carcinomas by immunohistochemistry, and analysed their involvement in disease progression.

Materials and methods

Patient population. A total of 58 cases of tongue carcinomas obtained at incisional biopsy or surgery at Meikai University Hospital (Sakado, Japan) from 1990 to 2010 were examined. The patients were comprised of 34 males and 24 females, with

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Key words: fatty acid-binding protein, progression, tongue carcinoma

Table I. Fatty acid-binding protein 5 staining score and clinicopathological parameters.

		Nucleus		Cytoplasm	
Parameters	No.	Mean ± SD	P-value[a]	Mean ± SD	P-value[a]
Age (years)			0.220		0.553
<65	33	4.969±2.495		8.188±2.571	
≥65	25	5.120±3.180		8.120±3.206	
Gender			0.491		0.411
Female	24	4.125±2.153		7.542±3.036	
Male	34	5.697±3.036		8.606±2.645	
T-stage[b]			0.137		0.125
T1	38	4.842±2.666		7.553±2.617	
T2	18	4.824±2.580		9.059±2.968	
T4	2	10.500±2.121		12.000±0.000	
N-stage[b]			0.482		0.764
N0	49	5.021±2.809		7.979±2.779	
N1	6	4.000±1.265		9.167±3.488	
N2	3	7.333±4.163		9.000±3.000	
Clinical stage[b]			0.720		0.619
1	38	4.842±2.666		7.553±2.617	
2	10	5.333±3.354		9.333±2.958	
3	6	4.000±1.265		9.167±3.488	
4	4	7.750±3.500		9.750±2.872	
Histological differentiation			0.463		0.161
Well	32	5.469±2.771		8.189±2.856	
Moderate	20	4.450±2.395		7.750±2.899	
Poor	6	4.600±4.334		9.600±2.510	

[a]Pearson's Chi-square test. [b]Patients were classified by tumor size (T-stage) and clinical stage according to the International Union Against Cancer World Health Organization grading system and by the stage of lymph node metastasis (N-stage).

an age range of 29-92 years (mean ± SD, 62.8±14.9 years) at the time of diagnosis. The details of pretreatment clinical and pathological characteristics are provided in Table I. Histologic grading and staging were assessed according to the International Union Against Cancer (UICC) tumor-node-metastasis classification. Tissues were obtained subsequent to the written consent of the patient and with the approval of the Ethics Committee of the Institutional Review Boards of Meikai University.

Mouse skin wounds. Mouse skin wound tissues were obtained as previously described (19). Briefly, 2 cm long full-thickness skin incisions were created on the dorsum of C57BL/6 female mice. The mice were sacrificed at 1, 3, 5, 7, 14 and 21 days after wounding and tissue samples were obtained from three different wounds at each time point. The animals were housed and used according to the Rules for the Care and Use of Laboratory Animal Guidelines of the Nippon Dental University under a protocol approved by the Institutional Review Board.

Immunostaining. Unstained formalin-fixed, paraffin-embedded carcinoma and mouse wound sections were incubated with rabbit anti-FABP4 (ab13979; Abcam, Tokyo, Japan) or rat anti-FABP5 (MAB3077; R&D Systems, Minneapolis, MN, USA) antibodies followed by biotinylated anti-rabbit or -rat IgG. Following treatment with avidin-biotin complexes, the color was developed with 3,3'-diaminobenzidine hydrochloride. The immunostaining of FABPs was evaluated as described previously (20). Briefly, the extent of staining was scored on a scale of 0-4: 0, totally negative; 1, <10%; 2, 10-40%; 3, 41-60%; or 4, >61%. Positive nuclear and/or cytoplasmic staining was subjectively classified as: 1, weak; 2, moderate; or 3, strong at the area of strongest staining due to the variable intensity of the staining. Weak staining was barely discernible and only clearly visible on high-power examination; moderate staining was easily seen at low power and was light brown in color; and strong staining was intense and dark brown with a painted-on appearance. An immunohistochemical composite score was calculated by multiplying the extent and intensity scores to give a value of between 0-12.

Statistical analysis. Pearson's Chi-square test was used to analyze the immunostaining score for clinicopathological parameters. The Wilcoxon signed-rank test was used to compare between the scores. $P<0.05$ was considered to indicate a statistically significant difference.

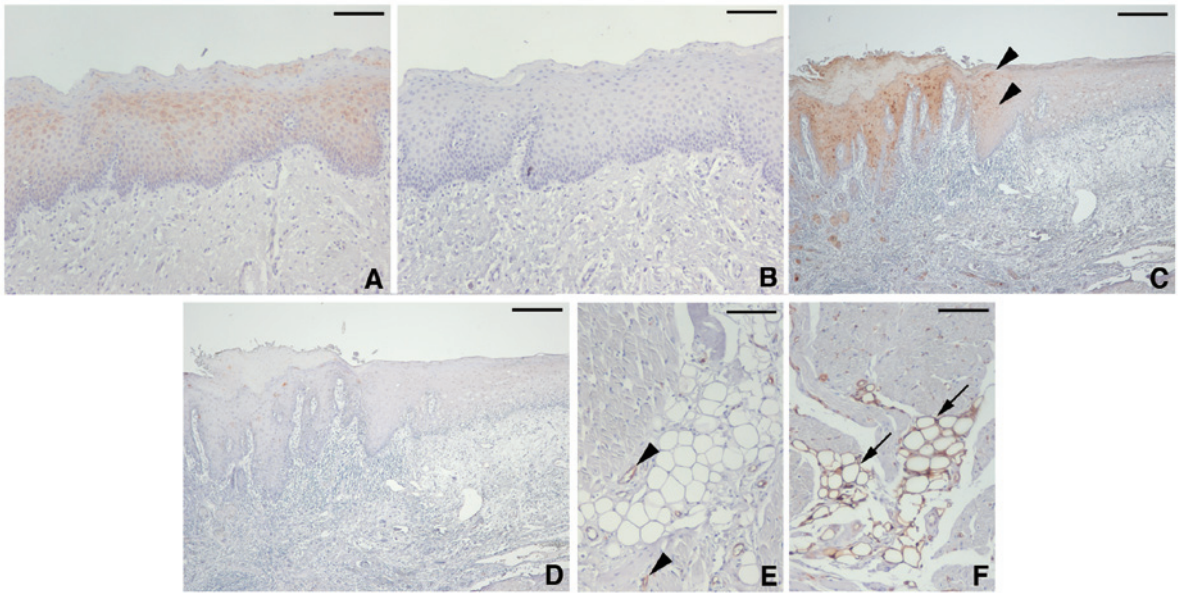

Figure 1. Fatty acid-binding protein (FABP) expression in normal and carcinoma-adjacent epithelium of the tongue. (A, C and E) FABP5 and (B, D and F) FABP4 were stained on (A and B) normal tongue epithelium and (C and D) epithelium interface with carcinomas. Epithelial cells adjacent to the carcinomas enhanced FABP5 staining (arrowheads). (E, arrowheads) FABP5 was stained at the endothelial cells and (F, arrows) FABP4 at adipocytes in dermis. Bar, (C and D) 100 μm and (A,B,E and F) 40 μm.

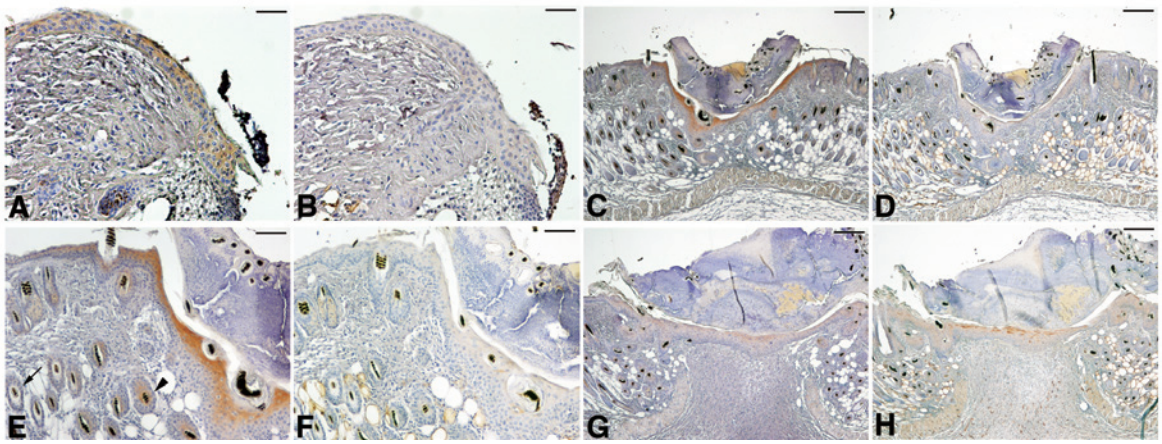

Figure 2. Fatty acid-binding protein (FABP) expression in skin wounds. (A, C, E and G) FABP5 and (B, D, F and H) FABP4 expression in mouse skin wounds at (A and B) day 1; (C-F) day 3; and (G and H) day 5 are shown. (E) The arrowhead and arrow show the hair follicle adjacent and far distal site of wounds, respectively. Bar, (C,D,G and H) 100 μm; (E and F) 40 μm; and (A and B) 20 μm.

Results

Expression and distribution of FABPs in a normal tongue. FABP5 expression was weakly detected at the cytoplasm of upper-suprabasal cells beneath the keratinized layer (Fig. 1A). FABP4 was not expressed in the normal epithelial cells of the tongue (Fig. 1B). At the epithelium, adjacent to carcinoma cells, FABP5-positive cells were extended to the suprabasal layer with a moderate-to-strong staining intensity (Fig. 1C), whereas FABP4 expression was negligible (Fig. 1D). The specificity of anti-FABP5 and -FABP4 antibodies was confirmed by the staining of endothelial cells (Fig. 1E) (21) and adipocytes (Fig. 1F) (8), respectively.

FABP expression in mouse skin wounds. The enhanced expression of FABP5 in the carcinoma-adjacent epithelium is suggestive of the fact that factors from the surrounding tissues or genetic alterations may activate FABP5 expression. Subsequently, FABP expression at the skin wounds of a genetically normal mouse was examined. As shown in Fig. 2, FABP5 expression was detected at the epithelial cells migrating on the wound surface at day 1. It became prominent at the cytoplasm of suprabasal cells at day 3 and gradually declined thereafter. FABP4 expression was slightly detected in the epithelium at day 3 but was negatively expressed at the earlier and later epithelium. The restricted detection of FABP5 on the skin epithelium and the strong staining of FABP4 on the subcutaneous adipocytes confirmed the specificity of antibodies to mouse FABPs.

FABP5 expression in tongue carcinomas. FABP5 expression was detected in all carcinoma tissues. It was preferentially

Table II. Fatty acid-binding protein 5 staining score in non-progressive/advanced stages of carcinomas.

		Nucleus		Cytoplasm	
Parameters	No.	Mean ± SD	P-value[a]	Mean ± SD	P-value[a]
T-stage[b]			0.357		0.041
T1	38	4.842±2.666		7.552±2.617	
T2-4	20	5.421±3.061		9.368±2.948	
N-stage[b]			0.355		0.383
N0	49	5.021±2.809		7.979±2.780	
N1-2	9	5.111±2.848		9.111±3.140	
Clinical stage[b]			0.357		0.041
1	38	4.842±2.666		7.553±2.617	
2-4	20	5.421±3.061		9.364±2.948	
Histological differentiation[c]			0.277		0.051
Well	32	5.469±2.771		8.188±2.856	
Less	26	4.480±2.771		8.120±2.877	

[a]Pearson's Chi-square test. [b]Patients were classified by tumor size (T-stage) and clinical stage according to the International Union Against Cancer World Health Organization grading system and by the stage of lymph node metastasis (N-stage). [c]Well, well-differentiated carcinomas; less, moderately and poorly differentiated carcinomas.

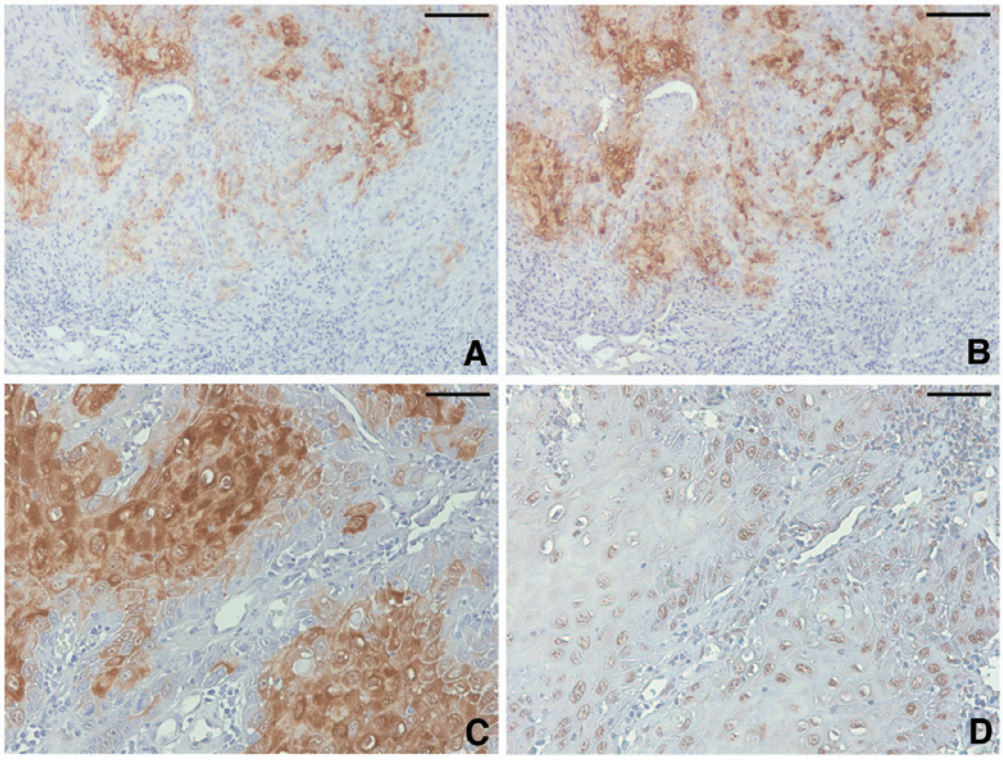

Figure 3. Fatty acid-binding protein (FABP) expression in tongue carcinomas. (A and C) FABP5 and (B and D) FABP4 were stained on the cytoplasm and/or nucleus of carcinoma cells. Bar, (A and B) 40 μm and (C and D) 20 μm.

observed at the cytoplasm of carcinoma cells, particularly at the center of tumor cell nests (Fig. 3A and C). The nuclear staining was weak and less frequent (mean ± SD, 5.035±2.790) compared with the cytoplasmic staining (8.158±2.840, P<0.001). The percentage (3.351±0.813) and staining intensity (2.439±0.598) scores of the cytoplasm suggest that tongue carcinoma cells frequently express FABP5 at a moderate-to-high level.

The correlation of the FABP5 staining score with the clinicopathological parameters was statistically evaluated (Table I). Although no significant difference was observed between them, the score increased in the advanced stages of

Table III. Fatty acid-binding protein 4 staining score and clinicopathological parameters.

		Nucleus		Cytoplasm	
Parameters	No.	Mean ± SD	P-value[a]	Mean ± SD	P-value[a]
Age (years)			0.099		0.194
<65	33	5.212±3.798		4.424±3.093	
≥65	25	4.400±2.972		4.360±2.752	
Gender			0.266		0.153
Female	24	4.208±3.134		4.083±3.269	
Male	34	5.324±3.649		4.618±2.686	
T-stage[b]			0.669		0.852
T1	38	4.737±3.629		4.211±2.849	
T2	18	4.833±3.222		4.722±3.268	
T4	2	7.500±2.121		5.000±1.414	
N-stage[b]			0.915		0.527
N0	49	4.837±3.490		4.347±2.803	
N1	6	3.333±1.751		4.000±4.336	
N2	3	8.333±4.041		6.000±2.000	
Clinical stage[b]			0.979		0.279
1	38	4.734±3.629		4.211±2.849	
2	10	5.100±3.247		4.900±2.846	
3	6	3.333±1.751		4.000±4.336	
4	4	7.750±3.500		5.500±1.915	
Histological differentiation			0.695		0.492
Well	32	5.094±3.762		4.250±2.771	
Moderate	20	4.300±2.812		4.850±3.281	
Poor	6	5.500±4.087		3.667±2.733	

[a]Pearson's Chi-square test. [b]Patients were classified by tumor size (T-stage) and clinical stage according to the International Union Against Cancer World Health Organization grading system and by stage of lymph node metastasis (N-stage).

the carcinomas. A number of observations at each stage of the parameters were variable, thus we divided patients into the advanced and non-advanced groups. The advanced group on the T- and clinical stages exhibited a significantly higher score compared with the non-advanced group (Table II).

FABP4 expression in tongue carcinomas. FABP4-positive cells are distributed randomly through carcinoma tissues and frequently located at peripheries of tumor cell nests where FABP5 staining was rapidly reduced (Fig. 3B). The percentage score of FABP4 cytoplasm-positive cells (2.368±1.057) and the staining intensity score (1.776±0.750) were low compared wiht that of FABP5 (percentage score, 3.351±0.813, P<0.001; staining intensity score, 2.439±0.598, P<0.001). Although the percentage and intensity of FABP4 nuclear staining was comparable with FABP5 (data not shown), FABP4 was frequently localized at the nucleus without the cytoplasmic staining (Fig. 3D). This exclusive nuclear staining was not observed in the FABP5 staining. No statistical difference was observed in the nuclear and cytoplasmic score for any of the clinicopathological parameters (Table III).

Discussion

FABPs transport LCFAs to the proper cell compartments and play a multifaceted role, particularly for lipid storage and β-oxidation in the cytoplasm and for transcription factor activation in the nucleus (8,9). Although FABP expression is restricted within the originally identified tissues, findings of a previous study emphasized that the aberrant expression is involved in carcinoma progression (8). In this study, we examined FABP4 and FABP5 expression in tongue carcinomas and identified a correlation between cytoplasmic FABP5 staining and disease progression.

The enhanced expression of FABP5 in epithelial cells at the skin wound edge and near carcinoma cells confirmed the findings of previous studies (22,23). Epithelial cells at the wound edge stimulate metabolic pathways (24) and its rapid proliferation and migration are key features in the early phase of wound healing (25,26). FABP5 is overexpressed in proliferating keratinocytes (27) and stimulates the proliferation and migration of oral carcinoma cells (11). Although the staining intensity was not strong, FABP5 expression was detected in wounds at day 1, suggesting the involvement of FABP5 in the

early phase of wound coverage. However, FABP5 promotes keratinocyte differentiation (28), as was evident by strong staining in the keratinizing suprabasal cells of wounded epithelium at day 3. These data confirmed the data of a previous study which demonstrated that FABP5 is markedly expressed in post-mitotic skin keratinocytes and weakly detectable in proliferating keratinocytes (29). Differentiating keratinocytes do not reside in the proliferation cycle (30). These paradoxical events suggest a multifaceted role and/or a biphasic action of FABP5 in the definition of cells depending on the situation.

The majority of cells positioned at or near carcinomas are associated with genetic alterations (31). The transient expression of FABP5 in the wounded skin of a genetically normal mouse indicates that epithelial cells upregulate FABP5 expression as a result of tissue reaction. This finding was supported by the intense staining at hair follicle cells near the wounds compared with the far distal follicle cells. It seems likely that carcinoma cells and the juxtaposed epithelial cells initiate the expression under the tissue reaction. Epidermal growth factor, a representative tissue factor, facilitates carcinoma progression (4) and skin wound healing (32) and overexpresses FABP5 (33). Other growth factors such as WNT and transforming growth factor-β, which stimulate progression and healing (34,35) regulate FABP5 expression (36,37). Since proteolytic degradation of the extracellular matrix releases growth factors (38), we should consider the impact of carcinoma cell-tissue interactions on the expression carefully. Furthermore, an intracellular signaling molecule, mucosa-associated lymphoid tissue 1, which suppresses the aggressive phenotype of oral carcinoma cells and is inactivated in the patients with worse prognosis directly affects FABP expression (39,40). Therefore both genetic and environmental factors provoke carcinoma cells to express FABP5.

The cytoplasmic FABP5 staining score was increased in carcinomas with the advanced T- and clinical stages in the current study. FABP5 transports LCFAs to mitochondria for energy production (8,9) and the increased production strongly facilitates the aggressive properties of carcinoma cells (7). Carcinoma progression (clinical stage) is a comprehensive issue evaluated by tumor expansion (T-stage) and metastasis (N- and M-stage). Since carcinoma metastasis is a consequence of various phenomena (4), the insignificance of expression in N-stage is unlikely to negate the role of FABP5 in carcinoma aggressiveness. Enhanced energy production by FABP5 may result in the rapid proliferation of carcinoma cells and tumor expansion.

The pathological role of FABP4 is largely different among carcinomas, as it is suppressive in bladder (17,41) and breast carcinomas (18) and stimulatory in gastric (14) and ovarian carcinomas (15). FABP4 expression was identified in almost all the tongue carcinomas examined. Although it was undetected in the normal epithelium, it is expressed by the suprabasal cells of wounded skin epithelium at day 5, although not the earlier and later wounds. This observation suggests that the expression in keratinocytes is not largely regulated by tissue factors. The FABP4 staining score did not correlate with oral carcinoma progression in the current study. FABP4, unlike FABP5, was frequently localized at the nucleus without the cytoplasmic staining. FABP4 transports LCFAs to the nucleus, which is required for stable binding with peroxisome-proliferator-activated receptor (PPAR)-γ. PPAR-γ expression in tongue carcinomas is higher in patients with an improved prognosis (42) and the administration of a PPAR-γ agonist inhibits the development of tongue carcinoma (43). However, oral carcinoma cells showing aggressive phenotypes *in vitro* strongly upregulate FABP4 expression (40,44). Detailed future studies are required in order to further clarify the role of ectopic expression.

FABP5 was mainly detected at the cytoplasm that was prominent in advanced tongue carcinomas. Enhanced expression may contribute to the production of sufficient quantities of energy that result in the progression of carcinomas to a more advanced stage. Identification of the mechanism of FABP5 upregulation and the pathological role in detail should therefore be analyzed for in order to improve patient prognosis.

Acknowledgements

This study was supported by an institutional grant from the Nippon Dental University (to K.I.) and by grants from JSPS KAKENHI (no. 22592080, to T.C.) and (no. 22592103, to K.I.); and based on a partial fulfillment of doctoral thesis submitted to the Graduate School of Dentistry, Meikai University, in partial fulfillment of the requirements for the Doctor of Dental Surgery degree.

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